Published by Elsevier Inc.

ISSN 0735-1097/03/$30.00

doi:10.1016/S0735-1097(03)00902-1

EDITORIAL COMMENT

Diabetes and Heart Failure: Is Insulin Therapy the Answer?*

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In this issue of the *Journal*, Guazzi et al. (1) report the very provocative effects of an acute insulin infusion on pulmonary function and exercise performance in patients with well-controlled type 2 diabetes (HgbA1C 6.2%) and heart failure (HF). Intravenous insulin (10 IU) had no effect on resting ejection fraction but did decrease resting systolic pulmonary artery pressure. Insulin improved resting lung diffusing capacity for carbon monoxide (DL_{CO}) and its subcomponents alveolar-capillary membrane diffusion capacity (D_M) and pulmonary capillary volume available for gas exchange (Vc). Insulin also had a marked effect on exercise with an increase in the workload and the oxygen consumption (VO_2) both at anaerobic threshold (AT) and peak exercise. There was also an increase in both aerobic (VO_2 increase per watt of work increase [VO_2/W]) and ventilatory efficiency (increase in ventilation with respect to carbon dioxide production [VE/VCO_2]). The changes persist at least 6 h. Peak VO_2, VE/VCO_2, VO_2/W, and DL_{CO} are all

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predictors of mortality in HF. However, which measurement is the best predictor of mortality in HF is uncertain. Can the effects of intravenous insulin be sustained and would this decrease the mortality in HF subjects with diabetes? Even more provocative, given the mild nature of the diabetes in these subjects, how would intravenous insulin affect HF patients without diabetes?

DL_{CO} varies with lung volumes, hemoglobin and, less well-known, cardiac output. In normal subjects, additional lung capillaries are recruited during exercise in proportion to the increased cardiac output and DL_{CO} can double. In HF, the resting DL_{CO} is reduced but it increases during exercise in proportion to cardiac output. In primary lung diseases like pulmonary fibrosis, there is an inability to recruit additional pulmonary capillaries and the DL_{CO} fails to increase during exercise (2). In HF, DL_{CO} also correlates with peak VO_2 and pulmonary vascular resistance (3). Guazzi et al. (1) reported that insulin increased the DL_{CO} and the change in DL_{CO} correlated with the improvement in peak VO_2 and VE/VCO_2. The magnitude of improvement in the peak VO_2 with insulin is similar to three months of exercise training. The change in peak VO_2 (~14%) is greater than angiotensin-converting enzyme inhibitors (minimal), beta-blockers (~ 0 to 5%), and cardiac resynchronization therapy (~7%). Although the authors noted a correlation between an improvement in DL_{CO} and both peak VO_2 and VE/VCO_2, they appropriately caution that this association may not be causal. In normal subjects, DL_{CO} is associated with rest cardiac index (4) but not peak VO_2 (5). DL_{CO} is unaltered by exercise training (6) and may worsen after cardiac transplant whereas peak VO_2 is increased (7). Angiotensin-converting enzyme inhibitors increase peak VO_2 and DL_{CO}, whereas hydralazine/nitrates have an even greater increase in peak VO_2 but the DL_{CO} is unchanged (8). It is more likely the change in peak VO_2 and VE/VCO_2 is secondary to improved endothelial function and redistribution of blood flow at the pulmonary and skeletal muscle capillary level and not a direct result of the change in DL_{CO}.

The Framingham study has shown diabetes increases the risk of developing HF twofold in men and fourfold in women (9). Conversely, patients with HF are at an increased risk of developing diabetes mellitus (10). The interrelationships of these observations are complex and uncertain but are probably due to neurohormonal and cytokine activation that is present in both diabetes and HF.

Patients with type 2 diabetes have low-grade inflammation with elevation of proinflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), endothelin 1, C-reactive protein, and norepinephrine (11). Insulin resistance is associated with a reduction in type I skeletal muscle fibers (12), reduced skeletal muscle blood flow, and glucose uptake during exercise (13), resulting in earlier anaerobic threshold and a reduced peak VO_2 (14,15). These changes at the skeletal muscle level may be mediated by reduced nitric oxide (NO)-mediated vasodilation or by alteration in substrate utilization with decreased skeletal muscle glucose oxidation (16). In sepsis, endotoxin activates proinflammatory cytokines, induces insulin resistance (17), and impairs left ventricular systolic function (18). Insulin has been proposed to be a potent antiinflammatory that suppresses TNF-α, IL-6, intercellular adhesion molecule-1, macrophage chemoattractant protein-1, and nuclear factor-κB (19) and enhances NO synthesis (20). In ventilated intensive care unit patients, 87% of whom did not have diabetes, an insulin infusion to normalize glucose to 80 to 110 mg/dl reduced markers of inflammation, infections, transfusions, and mortality (21).

Heart failure is an inflammatory state with elevation of many of the same neurohormones and cytokines as seen in type 2 diabetes, albeit at much higher levels (22). The cytokine elevations are prognostically important, especially IL-6 and TNF-α receptors (23). Interestingly, the beneficial effect of insulin on HF is not a new finding (24),

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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JACC Vol. 42, No. 6, 2003
September 17, 2003:1051–3

although previous investigations have focused on left ventricular performance rather than skeletal and pulmonary performance. The mechanisms for these findings are not clear. In HF, diabetes confers an additional risk of death, but whether this observation is independent of or mediated by alterations in exercise variables, neurohormones, and cytokines is uncertain (25). Is it possible the beneficial effects reported with insulin therapy in HF are related to its suppression of common cytokines, endothelin 1, free fatty acids, or norepinephrine, all of which also worsen insulin resistance?

In HF, there are marked alterations in the skeletal muscle, including a decrease in the efficient type I highly oxidative fibers, oxidative enzymes, and mitochondrial density and an increase in the inefficient type IIb glycolytic fibers as well as muscle and capillary atrophy (26). Diabetes has many of the same skeletal muscle changes along with impaired insulin-mediated glucose uptake by type I fibers (12). Insulin stimulates glucose uptake via GLUT4 in proportion to the oxidative capacity of the muscle fiber, type I > type IIa > type IIb (27). In animals and humans, the O_2 consumption in type I fibers is only 40 to 50% of type II fibers performing the same work (28). During exercise, there are alterations in the skeletal muscle fiber type recruitment and blood flow. At low levels of exercise, type I fiber utilization predominates (oxidative) and lactate levels are low. At levels of exercise above the anaerobic threshold, type II glycolytic fibers are recruited, which is associated with an increase in lactate production (29). Type I fibers are more sensitive than type II to the vasoconstrictor effects of norepinephrine (30) and to insulin-mediated glucose uptake (12). In HF and diabetes, it is anticipated that the high sympathetic activity and cytokines would divert blood flow from the efficient type I fibers to inefficient type IIb fibers whereas insulin would improve skeletal muscle blood flow (31) and glucose uptake predominantly by oxidative type I fibers (32).

Aerobic efficiency in HF is a complex interaction that requires the measurement of VO_2 during exercise and recovery. Previous investigators have suggested as HF progresses, there is a compensatory increase in aerobic efficiency as measured by a lower VO_2/W (33). However, HF patients are not more aerobically efficient (lower VO_2/W) but rather accumulate a large oxygen debt (recovery VO_2/W) that must be repaid after the completion of exercise such that the total oxygen cost of exercise which includes the recovery VO_2/W, is actually increased (34). Guazzi and colleagues report only the VO_2/W during exercise. It is anticipated that insulin improves skeletal muscle blood flow to type 1 fibers (31), possibly because of enhanced NO (20,35) and increased glucose uptake/oxidation (12,32). This permits a longer duration of "aerobic" exercise before the recruitment of type IIb glycolytic fibers. This is supported by the observation that all the increase in workload and VO_2 occurred from rest to AT whereas the workload and VO_2 from AT to peak was unchanged in the current study. It is further anticipated that the 21% improvement in aerobic efficiency will be accompanied by a similar decrease in the oxygen debt (34).

As previously noted, it is tempting to speculate about the effect of insulin in HF subjects with insulin resistance who do not have diabetes. If insulin has such a beneficial effect in HF, why has it taken so long to make this observation? Subcutaneous insulin has been used as a standard of care for over 80 years, and yet it has been only relatively recently that improvements in HF and myocardial infarction have been shown in clinical trials to be improved by insulin (36). Perhaps the answer is that cardiovascular benefit can be best attained using intravenous insulin as opposed to the more common subcutaneous insulin delivery. If this is the case, would intraperitoneal insulin delivery be an option for severe HF with diabetes? Implantable pumps for the treatment of diabetes are now being developed, but perhaps this is something that could also be used for HF. It seems to us that for there to be real progress in this area, advancement in two areas will be required. First, the findings of Guazzi et al. (1) need to be further clarified and the exact mechanisms of improvement with insulin in HF will need to be documented. Furthermore, cardiologists will need to work closer with endocrinologists to become more comfortable with the use of insulin, for both inpatients and outpatients. If we can succeed with both of these goals, there is the potential to make major contributions for this growing patient population.

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